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Iodine Metabolism and Thyroid Physiology: Current Concepts

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ABSTRACT

Iodine plays a central role in thyroid physiology, being both a major constituent of thyroid hormones (THS) and a regulator of thyroid gland function. This review concerns those aspects of thyroid physiology in which significant advances have been made in recent years. We have known for decades that the thyroid gland concentrates iodide (I^-) against an electrochemical gradient by a carrier-mediated mechanism driven by ATP. A similar I^- uptake mechanism is found in other organs, including salivary glands, stomach, choroid plexus, and mammary glands, but only in the thyroid does TSH regulate the process. This past year saw a major advance with the cloning of the thyroid I^- transporter. This development opens the way to an elucidation of the regulation of I^- transport in the normal gland and in thyroid neoplasms that lack this property ("cold" nodules). All of the subsequent steps in TH biosynthesis, from oxidation and organification of iodide to the secretion of T_4 and T_3 into the circulation, are stimulated by TSH and inhibited by excess iodine. Recently, some of the regulatory mechanisms have been clarified. The function of the major TH-binding proteins in plasma is to maintain an equilibrium between extracellular and cellular hormone pools. Transthyretin, the principal T_4-binding protein in cerebrospinal fluid, may play a similar role in the central nervous system. Although it generally is agreed that cellular uptake of TH is a function of the unbound (free) form of the hormone, there is evidence that certain TH-binding plasma proteins (i.e., apolipoproteins) may serve specific transport functions. The intracellular concentration of T_3, the active TH, is determined by the rates of cellular uptake of T_4 and T_3, the rates of metabolic transformation, including conversion of T_4 to T_3, and the rate of T_3 efflux. The latter has been assumed to be a passive process. However, recent studies by our group in San Francisco have shown that T_3 is transported out of cells by a specific, saturable, verapamil-inhibitable mechanism. This T_3 efflux system is widespread among cells from many tissues and, at least in liver, modulates intracellular and nuclear concentration of the hormone and thereby influences TH action.

INTRODUCTION

IODINE PLAYS a central role in thyroid physiology, being both a constituent of thyroid hormone and a regulator of thyroid gland function. This is a brief survey of iodine metabolism and thyroid hormone physiology, focusing selectively on some significant recent advances and citing when possible reviews rather than primary references.

Dietary iodine is absorbed efficiently in the gastrointestinal tract. Iodine in organic form is converted mostly to iodide before absorption. Fig. 1 shows a compartmental model of iodide distribution in the human, based in part on the work of Hays (1,2). Plasma iodide exchanges rapidly with iodide in red blood cells and with both rapid and slow extracellular compartments. Besides the thyroid, other organs that concentrate iodide include the salivary glands, gastric mucosa, choroid plexus, mammary glands, and the placenta. The enteric phase consists of iodide secreted into saliva and gastric juice, which moves into the small intestine for reabsorption. The kidneys account for about two-thirds of the iodide cleared from the plasma and more than 90% of iodide excreted from the body. Sweat and breast milk account for variable fractions of iodide loss. Hays (3) has presented evidence that iodide is secreted from the blood into the large bowel, which may explain partly why the colon often is seen in radioiodine scans in patients post-thyroidectomy. However, the fecal route contributes only about 1% of total body iodide clearance.

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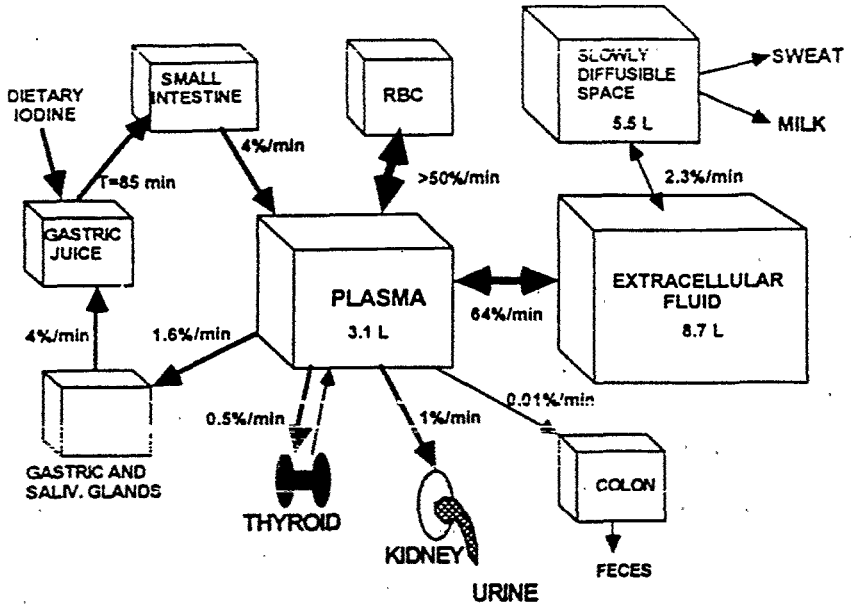

FIG. 1. A compartmental model of inorganic iodine distribution and clearance in humans, adapted from the work of Hays (1,2). The rates of exchange of iodide between compartments are given in % of the plasma iodide compartment transferred per minute. The rate of iodide transfer from stomach to small intestine is expressed as a mean transit time (T).

Fig. 2 shows a simplified schema of thyroid iodine metabolism (4). The follicular cell *in situ* displays functional and structural polarity; the iodide transporter resides in the basolateral plasma membrane, which also contains ATPases and various channels and receptors, including the TSH receptor (not shown). At the apical surface, thyroglobulin, thyroid peroxidase, hydrogen peroxide, and iodide all come together. Oxidation and organification occur at or near this cell-colloid interface. Hormone secretion involves, first, pinocytosis of colloid-containing iodinated thyroglobulin, then fusion of colloid droplets with lysosomes, followed by proteolysis, which liberates free monoiodotyrosine (MIT), diiodotyrosine (DIT), T_4, and T_3. Iodotyrosine dehalogenase regenerates iodide from MIT and DIT for reuse within the thyroid or release into the blood, accounting for the iodide leak in the chronic state of iodine excess and in certain thyroid disorders. Type I iodothyronine deiodinase converts some of the free T_4 into T_3. Both hormones are released into the circulation by a process that is not well understood. The thyroid also

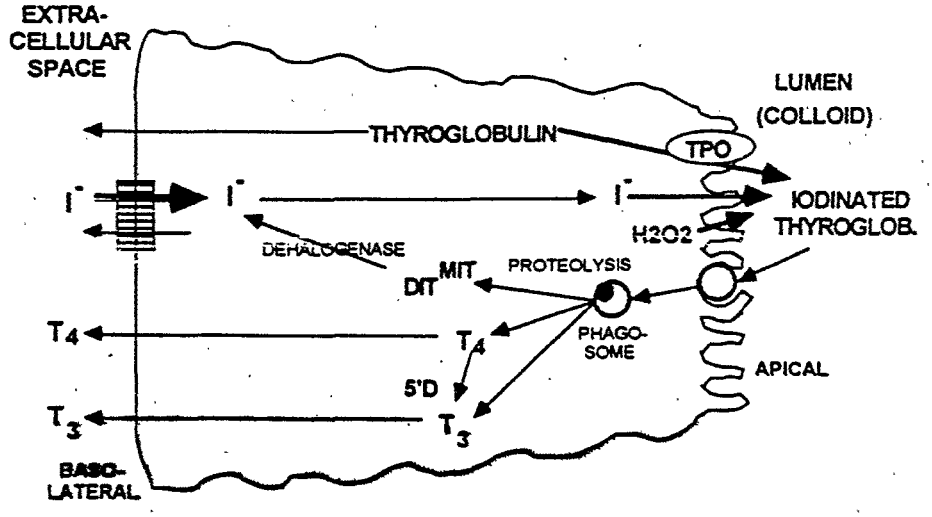

FIG. 2. A scheme of iodine metabolism and hormone biosynthesis in a single thyroid follicular cell. The vascular space is on the left, and the lumen of the follicle is on the right. The shaded box straddling the basolateral membrane represents the iodide transporter. At the apical surface, TPO stands for thyroid peroxidase, and H_2O_2 depicts the hydrogen peroxide generating system. 5'D is the Type I iodothyronine 5' deiodinase.

releases thyroglobulin, of which some is iodinated and some uniodinated, newly synthesized protein.

TSH stimulates every phase of thyroid iodine metabolism (5,6). Most of the effects of TSH are mediated by the G protein-adenylate cyclase-protein kinase A cascade. The TSH-induced stimulation of iodide uptake is a delayed effect and involves an increase in the maximum velocity of the iodide transport mechanism. This effect is blocked by inhibitors of RNA and protein synthesis, and therefore the TSH-induced stimulation of iodide transport has been assumed to involve increased gene expression (5). However, recent work suggests that the action of TSH may involve either translocation of the iodide pump from the interior of the cell to the plasma membrane or conversion of an inactive form of transporter in the plasma membrane to an active form (7). TSH also increases ATP production and ATPase activity. One of the earliest effects of TSH is to open the apical iodide channel to increase iodide efflux from cell to colloid. TSH increases the synthesis of thyroglobulin and thyroid peroxidase, via the cyclic AMP (cAMP) cascade acting at the level of transcription and possibly post-transcription as well. The stimulation of hydrogen peroxide production appears to involve the inositol-phosphate-calcium pathway at least in the human thyroid. The stimulatory effects of TSH on pinocytosis, proteolysis, and Type I deiodinase can be reproduced by cAMP. Secretion of thyroglobulin also is under TSH control (via the cAMP second messenger pathway). All of these manifold effects of TSH on thyroid function, of course, are mimicked by the stimulating anti-TSH receptor antibody of Graves' disease.

The supply of iodine regulates thyroid hormonogenesis and alters thyroid sensitivity to TSH. This has been termed "autoregulation" (8,9). Excess iodine exerts generally inhibitory effects, most of which are mediated by one or more still unidentified organic iodine compounds, probably iodolipids. There is a blunting of all TSH effects mediated by both second messenger cascades. The Wolff-Chaikoff effect, which is an acute iodine-induced inhibition of organification, appears to be mediated by decreased hydrogen peroxide production. Other effects of excess iodine include down-regulation of iodide transport, responsible for the escape from the Wolff-Chaikoff effect; increase in the ratio of iodotyrosines to iodothyronines in thyroglobulin; and acute inhibition of pinocytosis and proteolysis, resulting in decreased hormone secretion. This inhibition of colloid resorption, which involves steps both pre- and post-cyclic AMP, is the only effect of iodine shared by lithium (10).

Thyroid iodide uptake is basic to the clinical applications of radioiodine in diagnosis and therapy. Work in the early 1960s established that the thyroid iodide transport is saturable and specific and is linked to a sodium-potassium ATPase (11). It was shown subsequently that the driving force for iodide uptake against the electrical gradient is the transmembrane difference in sodium ion concentration generated and maintained by the sodium-potassium ATPase. The iodide pump itself is actually a sodium-iodide cotransporter, or symporter. Two sodiums are transported for each iodide ion that moves into the cell. Complex anions, such as perchlorate, competitively inhibit the iodide transporter. These and many other properties have been known for years, but until recently no one had isolated the iodide transporter.

The cloning of the rat sodium-iodide symporter is a major step forward (12). The putative structure of the rat sodium-iodide transporter, deduced from the nucleotide sequence of the isolated cDNA, includes 618 amino acids, 12 putative transmembrane domains, 3 charged residues, including an arginine in the sixth helix, and a consensus sequence for protein kinase A phosphorylation on the final intracellular loop near the carboxy-terminus. Jhiang and colleagues, using the cDNA sequence of the rat iodide transporter, recently isolated and cloned the human homologue (13). We now may expect rapid progress in finding answers to such questions as: What is the basis for the defect in iodide transport in "cold" nodules? What is the molecular mechanism by which TSH stimulates iodide transport in differentiated thyroid cancers?

Normal thyroid tissue incubated *in vitro* under conditions in which organification of iodine is blocked can generate a tissue-to-medium iodide gradient of 10 to 1 or more, whereas most solid cold thyroid nodules, both benign and malignant, are unable to generate any gradient at all (14,15). However, not all cold nodules show this type of defect. Some neoplasms concentrate iodide but cannot organify it (16). Either defect will shorten the effective half-life of iodine in the tumor. Goitrous or neoplastic thyroids may produce thyroglobulin abnormal in structure and iodine content (17,18). In addition, some tumors may produce large amounts of smaller iodinated proteins, like iodoalbumin. Rare cases of hyperthyroidism due to overproduction of hormone by differentiated thyroid carcinoma have been described. Perhaps these involve somatic mutations in the TSH receptor or G protein causing constitutive activation, similar to the activating mutations described in some toxic adenomas (19).

The physiologic role of plasma protein binding has been the subject of speculation ever since the discovery of thyroxine-binding globulin (TBG) in 1952. Robbins and Rall, who formulated in mathematical terms the free hormone hypothesis, postulated that plasma binding proteins, TBG in particular, provide a circulating reservoir of thyroid hormone and a buffer against drastic and abrupt changes in free hormone concentration. None of the three major thyroid hormone binding proteins (TBG, transthyretin, and albumin) is essential for life (20).

Further insight and support for the free hormone hypothesis was provided by Mendel and colleagues (21), using a liver perfusion system to show that, in the absence of any binding protein in the perfusing medium, both T_4 and T_3 are taken up rapidly and retained by the first cells encountered. In contrast, in the presence of binding protein, hormone is distributed uniformly throughout the organ. Thus, the binding proteins, by limiting the fractional uptake into cells, ensure equilibrium between cellular and extracellular compartments. It has been suggested that transthyretin, which is the major T_4 binder in the cerebrospinal fluid, may play a similar role in ensuring uniform distribution of the hormone throughout the central nervous system (20).

These considerations do not exclude the possibility that certain binding proteins may target hormone to specific

sites in the body. For example, Benvenga and Robbins (22) have shown that human apolipoproteins mediate the uptake of T_4 (but not T_3) by fibroblasts containing low-density lipoprotein receptors. We do not yet know the physiologic importance of this type of cellular uptake mechanism.

The intracellular T_3 concentration largely determines the degree of occupancy of nuclear T_3 receptors and thereby regulates the biologic responses to thyroid hormone (23). Some factors that determine intracellular T_3 concentration are the rates of uptake of T_4 and T_3 from the extracellular fluid by passive diffusion or via stereospecific, energy-requiring uptake mechanisms (24). Further, the hormones undergo conjugation, oxidative decarboxylation, and deamination, but the major metabolic pathway is deiodination, which results in either activation or inactivation of hormone and plays an important role in overall thyroid hormone economy and in modulation of thyroid hormone levels in specific tissues.

The deiodination of iodothyronines is carried out by a family of selenoprotein enzymes. The Type I enzyme was cloned in 1991 (25). Subsequently, the Dartmouth group reported the cloning of the Type III deiodinase (26) and, recently, the human and rat Type II enzyme (27). In the euthyroid individual the Type I enzyme, present in liver and kidney, converts T_4 to T_3 and, even more efficiently, reverse-T_3 to T_2. The sulfoconjugates of T_4 and T_3 are preferred substrates for 5-deiodination by the same enzyme. The Type II 5'-deiodinase generates T_3 from T_4 in brain, pituitary, and brown adipose tissue. Recent data from two laboratories indicate that in the human (but not the rat), cardiac and skeletal muscle contain Type II deiodinase and may be a major source of circulating T_3 (27,28). The Type III 5-deiodinase converts T_4 and T_3 to their inactive derivatives and thus modulates the T_3 level in the brain and serves to protect the fetus from excessive amounts of the hormone (29).

In the low-T_4 state, the Type I (in liver and kidney) and Type III are down-regulated and Type II activity is increased, thereby tending to conserve T_3 in vital organs, such as the brain. The exception is the Type I enzyme in the thyroid, which becomes more active, accounting in part for the high ratio of T_3 to T_4 secreted from the TSH-stimulated gland, as, for example, in early thyroid gland failure (29).

Finally, the rate of efflux of hormone from the cell theoretically can affect the steady-state cellular T_3 level. Few studies have addressed outward transport as a process distinct from uptake, and until recently there have been no data indicating that thyroid hormone efflux is carrier-mediated or that it can affect hormone action.

Ribeiro and colleagues (30) recently have published evidence that in mammalian cells a saturable, specific, temperature-sensitive, verapamil-inhibitable T_3 efflux mechanism influences cellular T_3 concentration and responsiveness to T_3, presumably by controlling access of the hormone to nuclear receptors. The T_3 export process was demonstrated initially in rat heparoma cells, which were adapted specially for resistance to a bile acid ester and which overexpress several apparently novel ATP-binding cassette (ABC) proteins of the family of multi-drug resistant (MDR) P-glycoproteins. Verapamil-inhibitable T_3 efflux also was found in primary rat hepatocytes, cardiocytes, and fibroblasts. In hepatoma cells and primary hepatocytes, verapamil had no effect on T_3 uptake. The reversible inhibition by verapamil suggests that one or more ABC/MDR-related proteins are involved. These results suggest that T_3 extrusion from cells is a regulated process distinct from T_3 entry, providing an additional mechanism that, by controlling access of thyroid hormone to nuclear receptors, influences hormone action (30).

Virtually all of the advances in thyroid physiology made during the past half century—from the first quantitative measurements of radioiodine uptake by the thyroid gland to the subsequent discovery of T_3 and the demonstration of the complex regulation of thyroid hormone synthesis, secretion, transport, cellular metabolism, and hormone action—were possible because of the availability to investigators of radioiodine tracers.

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REFERENCES

1. Hays MT, Wegner LH 1965 A mathematical and physiological model for early distribution of radioiodide in man. J Appl Physiol 20:1319–1328.
2. Hays MT 1984 Compartmental models for human iodide metabolism. Math Biosciences 72:317–335.
3. Hays MT 1993 Colonic excretion of iodide in normal human subjects. Thyroid 3:31–35.
4. Taurog A 1996 Hormone synthesis. In: Braverman LE, Utiger RD (eds) The thyroid. A fundamental and clinical text, 7th ed. Lippincott-Raven, Philadelphia, p. 47.
5. Dumont JE, Vassart G 1995 Thyroid Regulation. In: DeGroot LJ (ed) Endocrinology, vol 1. WB Saunders, Philadelphia, p. 543.
6. Rapoport B, Spaulding SW 1996 Mechanism of action of thyrotropin and other thyroid growth factors. In: Braverman LE, Utiger RD (eds) The thyroid: A fundamental and clinical text, 7th ed. Lippincott-Raven, Philadelphia, p. 207.
7. Kaminsky SM, Levy O, Slavador C, et al. 1994 Na+-I-symport activity is present in membrane vesicles from thyrotropin-deprived non-I-transporting cultured thyroid cells. Proc Natl Acad Sci USA 91:3789–3793.
8. Ingbar SH 1972 Autoregulation of the thyroid: The response to iodide excess and depletion. Mayo Clin Proc 47:814–823.
9. Nagataki S, Yokoyama N 1996 Autoregulation: Effects of iodide. In: Braverman LE, Utiger RD (eds) The thyroid: A fundamental and clinical text, 7th ed. Lippincott-Raven, Philadelphia, p. 241.
10. Williams JA, Berens SC, Wolff J 1971 Thyroid secretion in vitro: Inhibition of TSH and dibutyryl cyclic-AMP stimulated ^{131}I release by Li^+. Endocrinology 88:1385–1388.
11. Carrasco N 1993 Iodide transport in the thyroid gland. Biochim Biophys Acta 1154:65–82.
12. Dai G, Levy O, Carrasco N 1996 Cloning and characterization of the thyroid iodide transporter. Nature 379:458–460.
13. Smanik PA, Liu Q, Furminger TL, et al. 1996 Cloning of the human sodium iodide symporter. Biochem Biophys Res Com 226:339–345.

14. DeGroot LJ 1970 Lack of iodide trapping in "cold" thyroid nodules. Acta Endocrinol Panam 1:27–31.
15. Field JB, Larsen PR, Yamashita K, et al. 1973 Demonstration of iodide transport defect but normal iodide organification in nonfunctioning nodules of human thyroid glands. J Clin Invest 52:2404–2410.
16. Valenta J 1966 Metastatic thyroid carcinoma in man concentrating iodine without organification. J Clin Endocrinol Metab 26:1317–1324.
17. Dunn JT, Ray SC 1978 Variations in the structure of thyroglobulins from normal and goitrous human thyroids. J Clin Endocrinol Metab 47:861–869.
18. Schneider AB, Ikekubo K, Kuma K 1983 Iodine content of serum thyroglobulin in normal individuals and patients with thyroid tumors. J Clin Endocrinol Metab 57:1251–1256.
19. Parma J, Duprez L, Van Sande J, et al. 1993 Somatic mutations in the thyrotropin receptor gene cause hyperfunctioning thyroid adenomas. Nature 365:649–651.
20. Robbins J 1996 Thyroid hormone transport proteins and the physiology of hormone binding. In: Braverman LE, Utiger RD (eds) The thyroid: A fundamental and clinical text, 7th ed. Lippincott-Raven, Philadelphia, p. 96.
21. Mendel CM 1989 The free hormone hypothesis: A physiologically based mathematical model. Endocrinol Rev 10:232–274.
22. Benvenga S, Robbins J 1990 Enhancement of thyroxine entry into low density lipoprotein (LDL) receptor-competent fibroblasts by LDL: An additional mode of entry of thyroxine into cells. Endocrinology 126:933–941.
23. Brent GA 1994 The molecular basis of thyroid hormone action. N Engl J Med 331:847–853.
24. Krenning EP, Docter R 1986 Plasma membrane transport of thyroid hormone. In: Hennemann G (ed) Thyroid hormone metabolism. Marcel Dekker, New York, p. 107.
25. Berry MJ, Banu L, Larsen PR 1991 Type I iodothyronine deiodinase is a selenocysteine-containing enzyme. Nature 349:438–440.
26. Croteau W, Whittemore SL, Schneider MJ, St. Germain DL 1995 Cloning and expression of a cDNA for a mammalian Type III iodothyronine deiodinase. J Biol Chem 270:16569–16575.
27. Croteau W, Davey JC, Galton VA, St. Germain DL 1996 Cloning of the mammalian Type II iodothyronine deiodinase. A selenoprotein differentially expressed and regulated in human and rat brain and other tissues. J Clin Invest 98:405–417.
28. Salvatore D, Bartha T, Harney JW, Larsen PR 1996 Molecular and biochemical characterization of the human Type 2 selenodeiodinase. Endocrinology 137:3308–3315.
29. St. Germain DL 1994 Iodothyronine deiodinases. Trends Endocrinol Metab 5:36–42.
30. Ribeiro RCJ, Cavalieri RR, Lomri N, et al. 1996 Thyroid hormone export regulates cellular hormone content and response. J Biol Chem 271:17147–17151.

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